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TITLE: **Randomized Controlled Trial of Sertraline, Prolonged Exposure Therapy and their Combination in OEF/OIF Combat Veterans with PTSD**

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14. ABSTRACT

The current proposal aims to directly compare the psychotherapy and medication treatments for PTSD considered to have the most evidence for effectiveness. While both SSRI and PE have demonstrated efficacy, there are significant individual differences in clinical responses to both treatments. To achieve best clinical outcomes and to utilize available treatment most effectively, it is critical to examine how PTSD and related psychopathology and functional impairment change with these treatments alone and in combination. Further, in order to inform clinical practice, we plan to examine psychological and neurobiological predictors of response to treatment and mechanisms of change during treatment (pre to post treatment change) based on previously identified predictors, including emotion regulation and processing with fMRI in response to emotional challenge tasks, DNA and mRNA (pre and post treatment), and cortisol response to awakening.
The primary activity and focus this year has been on recruitment and retention. We obtained funding to expand to 2 new CBOCs that are under the coverage of current IRBs. We were also approved for a 1-year no cost extension. Completion of study research and treatment protocol is our primary focus for the coming year. As of 12/21/15, we have recruited and randomized 203 Veterans and 92 Veterans have completed the Week 52 final study assessment visit.

15. SUBJECT TERMS
PTSD, Treatment, Medication, Therapy, fMRI, Cortisol

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INTRODUCTION

PTSD is a major public health concern and a growing problem for the VA and the DOD [1, 2]. Soldiers returning from Afghanistan and Iraq show PTSD rates of between 12 to 20% [3-6] with significant psychological, physical, and economic burdens for sufferers and society as a whole [7, 8]. Based on available treatment guidelines [9], the two first line treatments for PTSD include exposure therapy (such as PE) and selective serotonin reuptake inhibitors (SSRIs; such as SERT). To date, there have been no randomized, direct comparisons of medication, psychotherapy, and combined treatment among veterans or active duty troops. The current study aims to provide this critical data in a typical sample of OEF/OIF returnees with significant combat-related PTSD. Further, emphasis is placed on continued, comprehensive collection of outcome data to assess the acceptability, adherence, compliance, and symptom change in each treatment arm throughout the study period. In addition, substantial morbidity remains in a high percentage of PTSD veterans [10, 11] even after PE or SSRI treatment are administered, suggesting that further treatment optimization and individual treatment matching are urgently needed if substantial personal and social costs are to be reduced. Identifying specific predictors, large effect size correlates of treatment response, or putative mechanisms involved in treatment response will be critical steps toward achieving the goals of treatment optimization and individual treatment matching. To inform treatment choices beyond what can be provided through standard clinical outcomes, we will examine neurobiological predictors and proximal correlates of effective treatment, and candidate mechanisms involved. Delineation of these factors and their specificity to medication or PE is a critical step towards treatment refinements, improved effectiveness and efficiency of PTSD treatment, enhanced dissemination, and individualized treatment. This is obviously an ambitious set of goals; however, the combined expertise of the research group involved, the synergy of the aims, and the efficient design offer both a unique opportunity to examine multiple processes simultaneously, and to obtain the highest quality of critically needed data. To restrict the examination to just one system or one mechanism would be a missed opportunity to study these complex and interrelated systems and their interacting in impacts on treatment.

KEYWORDS

PTSD, Veterans, Prolonged Exposure, Sertraline, OEF, OIF, OND, treatment, therapy, medication, fMRI, cortisol

OVERALL PROJECT SUMMARY

This project will consist of seven primary tasks to be accomplished over the funding period at four sites: Veterans Affairs Ann Arbor Healthcare System (VAAAHS) /University of Michigan (UM), VA San Diego Healthcare System (VASDHS)/University of California San Diego (UCSD), Ralph H. Johnson Veterans Affairs Medical Center (RHJVAMC)/ Medical University of South Carolina (MUSC), and Massachusetts General Hospital (MGH)/Harvard Medical School.

SOW Task 1: (COMPLETE) Start-up activities and regulatory approvals

- Primary site (VAAAHS/UM) obtained full approval at VA Ann Arbor Healthcare System (Dec 2010), University of Michigan (Dec 2010), and HRPO (Jun 2011).
- MGH obtained full approval from MGH (Aug 2011) and HRPO (Sep 2011).
- RHJVAMC/MUSC obtained full approval from the MUSC IRB (Jul 2011), the VA R&D Committee (Aug 2011), and HRPO (Feb 2012).

- VASDHS/UCSD obtained full approval from UCSD IRB (May 2011), the VA R&D Committee (Sep 2011), and HRPO (Apr 2012).
- All sites have key positions hired in order to begin recruitment.
- Payment processes in place and being fulfilled in a timely manner.
- Subawards completed.

SOW Task 2: Training of study faculty and staff (initial completed; ongoing training related to staff turnover)

- All sites have key positions hired and trained in order to recruit patients.
- Study PI, Dr. Sheila Rauch moved from VAAAHS and UM to the Atlanta VAMC and Emory University in 2015Q2. To ensure minimal interruption of study conduct the following plan was implemented. The study continues to be administered through VERAM and Dr. Rauch remains the Principal Investigator for the study. She has maintained her status at VAAAHS (Research Investigator-Without Compensation) as well as UM (adjunct appointment) which allows her to maintain the role of study PI and keep VAAAHS/UM as the overall coordination site. Dr. Katherine Porter (VAAAHS) has been a critical study team member since study start (Study Psychotherapist, Multi-site Lead for Evaluation, on-site supervisor for clinical services). She became the Site PI to fill the on-site leadership role at VAAAHS that Dr. Rauch will not be able to accommodate from Atlanta (includes supervision for clinical crises or patient issues, problem solving site specific recruitment, etc.). In addition, Ms. Margaret Venners (VAAAHS) who has served as the Lead Study Coordinator for all study sites, remains in that role and leads the daily conduct of the study under the direction of Dr. Rauch and Dr. Porter. Dr. Rauch holds daily check-in phone calls with Ms. Venners to ensure things are running smoothly and address issues on-line as they come up. This is much more frequent than they previously met; however it was intended to prevent issues from escalating during the transition. Dr. Rauch has weekly calls with Dr. Porter and additional calls as needed. Finally, VAAAHS has an excellent senior study staff who continued in their roles including their Pharmacotherapists, Dr. Brian Martis, Mr. Sean Gargan, NP and a second Psychotherapist, Dr. Kimberly Avallone to ensure a smooth transition that was completed in 2015Q3.
- Additional staff changes and training completed this year include:
    - The Data Manager, Ms. Mandana Gholami left the study in 2015Q2 and her effort was transferred back to the DCC Data Programmer, Ms. Kathleen Wilcox-Pelzer.
    - Ms. Caitlin Authier (VAAAHS/UM) was promoted from Research Assistant to Study Coordinator to replace Ms. Mahrie Defever who left the study in 2015Q2.
    - Ms. Josephine Juanamarga was hired as a Study Coordinator in 2015Q3 to replace Ms. Kelly Knowles who left to pursue graduate studies.
    - Mr. Daniel Jones (VAAAHS/UM) who served as one of the original Independent Evaluators for the site left the study in 2015Q3 for his clinical internship. His effort will be covered by the other Independent Evaluator, Ms. Lauren McSweeney.
    - The site hired Mr. Barry Eye as an intermittent, back-up evaluator in 2015Q4 who is in the process of completing his training in case Ms. McSweeney is unblinded to a patient's treatment condition.
    - RHJVAMC/MUSC hired Ms. Martina Radic, Ms.Tina Kulhmann, Ms. Tatiana Eversley, Ms. Stephanie Zeigler and Ms. Jacelyn Lane as the site is now recruiting and seeing patients out of 3 locations: Savannah, GA, Hinesville, GA, and Charleston, SC, which are under the coverage of current IRB for the site.
    - MGH hired a new Research Assistant, Ms. Madelyn Frumkin in 2015Q2.

- Ms. Erica Vargas (VASDHS/UCSD) was hired in 2015Q3 to assist the full-time Study Coordinator, Mr. Mark West, who had an unexpected family emergency in July 2015 that resulted in him only being available part-time.

- Ongoing training and education efforts:
  - Weekly study team conference calls continue to be held to discuss logistical and procedural matters alternating between full study team, PI's &Co-I's, and study coordinators.
  - Dr. Naomi Simon leads monthly Pharmacotherapy calls.
  - Dr. Peter Tuerk leads weekly Psychotherapy calls.
  - Dr. Katherine Porter and Dr. Kimberly Avallone lead bi-monthly recalibration Independent Evaluator calls.

SOW Task 3: (COMPLETE) Set up study forms and refine all procedures

- All study forms are complete and in use at all sites.
- The Data Coordinator Center (DCC) completed the data validation checklist in 2012Q2. This checklist drives the process for identifying discrepant or missing data. A query and resolution process has been designed to document and resolve these issues using electronic Data Clarification Forms (eDCFs) sent by the DCC. This data clarification and resolution process occurs on a monthly basis.
- Laboratory procedures are finalized – supplies ordered and shipments sent to sites for initial recruitment.
  - Lab supply ordering procedures are established and in use.
  - Packaging and shipping procedures for lab samples finalized.
- fMRI protocol finalized.
  - Off-site travel participant procedures finalized. Participants have successfully traveled and been reimbursed.

SOW Task 4: Recruit and randomly assign Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn (OEF/OIF/OND) returnees with combat related Posttraumatic Stress Disorder (PTSD) to PE+ placebo (PE/PLB), sertraline + enhanced medication management (SERT), or PE + sertraline (PE/SERT)

As of 12/21/2015	Screened	Consented	Randomized
VAAAHS/UM	445	72	38
MGH	225	69	37
RHJVAMC/MUSC	443	203	87
VASDHS/UCSD	245	66	41
TOTAL	**1358**	**410**	**203**
Combat Controls	N/A	53	26

SOW Task 5: Conduct neurobiological mechanism study including assessment of genetics/genomics, brain function (first 210 interested participants), and hypothalamic–pituitary–adrenal (HPA) axis function

- Recruitment for the neurobiological mechanism study (fMRI substudy) began with overall study start in 2012Q1.
- As of December 21, 2015, 157 patients have consented to the fMRI substudy.

- 57 are enrolled (26 from VAAAHS/UM, 6 from MGH and 20 from RHJVAMC/MUSC, 5 from VASDHS /UCSD).
    - 57 patients have completed the pre-scan (Intake).
    - 29 patients have completed the post-scan (Week 24).
    - 12 are still in treatment phase.
    - 16 did not complete the fMRI post scan due to time constraints or were lost to follow up. We are working to reduce this number by ensuring people who consent for fMRI are aware of the need for post treatment scan and time required. Note that all 16 patients were study drops, not just the fMRI substudy.
- We continued our expanded availability for the fMRI substudy to include evenings and weekends as well as increased compensation. This has increased the number of off-site participants in addition to helping with retention.
- The discrepancy between number of patients enrolled versus the number consented is due to the size limitations of the bore diameter of the fMRI scanner (60cm). Study sites outside of Ann Arbor have been instructed to take a conservative approach to screening patients for fMRI procedures to attenuate the possibility of having costs for patients traveling to Ann Arbor whom may not be able to participate due to these parameters.

SOW Task 6: Follow-up of all returnees for one year from treatment initiation

- As of December 21, 2015, 126 patients have completed Week 24, 108 patients completed Week 36 research assessment and 92 patients have completed Week 52.

SOW Task 7: Data cleaning, initial statistical analyses, and dissemination of results

- Data cleaning is ongoing through the use of the eDCFs noted above in Task 2. 1087 new eDCFs were generated and have been resolved as of 12/21/2015.
- The DCC began reviewing and finalizing completed patients by locking patient data that has been monitored and cleaned in 2015Q3.
- Monitoring of a sample of data of all sites is completed by the study monitor to ensure data quality.
- A Progress study publication policy and procedure was finalized in 2015Q2 and has been implemented.
- Projects based on cross-sectional baseline data began this year and will continue in coming year.
- Given the analytic plan and power calculations for the study, interim analyses have not yet been completed.

Delays/Challenges/Barriers

- Recruitment challenges.
    - Barriers to recruitment:
        - Our biggest obstacle to recruitment is built into the design of the study in that we need Veterans willing to have psychotherapy and/or medication who are not currently on an antidepressant.
        - Patients not meeting eligibility criteria and/or meeting exclusion criteria.
            - Currently taking or having a failed trial of sertraline.
            - Not having combat-related PTSD.
            - Veterans that did not meet full criteria for a PTSD diagnosis.

        - Veterans not returning phone calls made as a follow-up to referrals.
        - Many Veterans from other eras are interested but not able to participate.
    - Additional recruitment efforts ongoing at all sites. Sites closely monitored for underperformance and areas of improvement. All sites have improved retention, though continued efforts to reach targets remain necessary. We are diligently working to retain resources in order to continue recruitment in the no-cost extension.

KEY RESEARCH ACCOMPLISHMENTS

- Randomized 203 patients to treatment as of 12/21/2015.
- 92 patients have completed the final study assessment visit (Week 52).
- 26 Combat Controls completed.
- Established consistent procedures for the outcome and mechanisms data across sites.
- Collecting all neurobiological and symptoms data from all sites through the centralized data center.
- Addition and start-up of 3 new recruitment locations: Charleston, SC, Hinesville, GA, and Toledo, OH.
- Implemented VA Clinical Video Telehealth (CVT) to conduct treatment (medication and therapy) visits and research assessments with patients at Community Based Outpatient Clinics (CBOCs). Provisions for PTSD treatment and assessment visits via CVT are now standard of care at the VA.
- Fidelity monitoring is underway.
- Created a logo to brand the study to increase awareness and focused recruitment efforts on providers by handing out promotional items in order to increase referrals and enrollment and retention at each site.
- Completion of the 7th DSMB meeting in December 2015 concern with recruitment rate but no major issues.

CONCLUSION

- Data collection is ongoing with preliminary analyses of pre-treatment fMRI and biological aims data underway. Our primary focus will continue to be recruitment and retention at all sites. Study is moving forward with data collection as planned with high quality measures. Data cleaning is ongoing. Study monitoring is underway with reported high levels of compliance with study procedures at all sites.

PUBLICATIONS, ABSTRACTS, PRESENTATIONS

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INVENTIONS, PATENTS AND LICENSES

Nothing to report.

REPORTABLE OUTCOMES

Nothing to report.

OTHER ACHIEVEMENTS

Nothing to report.

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APPENDICES

Nothing to report.